Title: Clinical outcomes according to QRS duration and morphology in the irbesartan in patients with heart failure and preserved systolic function (I-Preserve) trial

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ABSTRACT

Background: The aims of this study were to describe the prevalence of QRS prolongation and abnormal QRS morphology in patients with heart failure and preserved ejection fraction (HF-PEF) and to examine the relationship between these QRS abnormalities and clinical outcomes.

Methods: We categorized patients in the Irbesartan in Patients with Heart Failure and Preserved Ejection Fraction trial (I-Preserve) according to QRS duration <120 vs. e 120 milliseconds and QRS morphology: normal, left bundle branch block (LBBB) and right bundle branch block (RBBB) or other non-specific intra-ventricular conduction defect (IVCD). The outcomes examined were the composite of cardiovascular death or heart failure hospitalization (and its components) and all-cause mortality.

Results: Of the 4128 patients enrolled in I-Preserve, 3754 were included in the current analyses. 606 patients had a QRS duration e 120 milliseconds. 302 had LBBB and 742 had RBBB/IVCD. Patients with an abnormal QRS had evidence of more severe heart failure (lower LVEF, lower eGFR, higher NT pro-BNP) and worse clinical status (higher NYHA functional class, greater use of diuretics). Both abnormalities of QRS duration and QRS morphology were associated with worse outcomes. The rates of the composite outcome were: 6.0 and 9.3 per 100 patient years in the <120 and e 120 millisecond groups, respectively (adjusted hazard ratio [HR] 1.32, 1.11-1.57; P=0.002) and 6.0, 7.7 and 8.7 per 100 patient years in the normal, non-LBBB and LBBB groups respectively (adjusted HR 1.19, 1.00-1.42; P=0.046 and 1.31, 1.03-1.66; P=0.026, respectively, compared with normal). The heightened risk related to QRS abnormalities persisted after adjustment for other prognostic variables, including NT pro-BNP.

Conclusion: We found that both prolongation of QRS duration and abnormal QRS morphology were associated with a high risk of fatal and non-fatal adverse outcomes in HF-PEF.

Key words: Clinical trial, Heart failure, Preserved ejection fraction, Irbesartan

INTRODUCTION

The prognostic importance of QRS duration and morphology on the 12 lead electrocardiogram (ECG) in patients with heart failure and reduced ejection fraction (HF-REF) is well recognised.[1-4] Prolonged QRS duration and bundle branch block (BBB) are surface markers of dys-synchronous left ventricular contraction which is associated with worse outcomes in patients with HF-REF. [1-4] As such, these ECG parameters are used to identify patients who may benefit from cardiac resynchronization therapy.[5,6]

However, little is known about the prognostic importance of QRS duration and morphology in patients with chronic heart failure and preserved ejection fraction (HF-PEF).[7,8] Whether prolonged QRS duration and/or BBB is associated with worse heart failure outcomes in these patients has not been determined although, recently, left ventricular systolic dys-synchrony has also been demonstrated in HF-PEF patients, particularly in those with a wide QRS duration.[9] The aims of this study were to describe the prevalence of QRS prolongation and abnormal QRS morphology and examine the relationship between these QRS abnormalities and fatal and non-fatal heart failure outcomes in the Irbesartan in Heart Failure with Preserved Ejection Fraction (I-PRESERVE) trial.[10]

METHODS

The design, baseline characteristics and results of I-Preserve are published.[10,11] Briefly, 4128 patients aged e 60 years with a left ventricular ejection fraction (LVEF) e 45%, current signs and symptoms of heart failure and corroborating evidence (relevant electrocardiographic, chest X-ray or echocardiographic abnormalities) were randomized to 300mg once daily of irbesartan or placebo. Patients in New York Heart Association (NYHA) functional classes II to IV were eligible but those in class II were required to have had a hospitalization for heart failure within the previous 6 months. Ethics committees at each participating institute approved the trial and all patients provided written informed consent. The mean follow-up was of 49.5 months. No significant difference was seen in the primary composite outcome of death from any cause or hospitalization for a CV cause, or in any of the pre-specified secondary endpoints.

QRS duration and morphology: Investigators were asked to provide a report of the patient's ECG at the trial-screening visit using a structured case report form. This form asked about the QRS width (reported in milliseconds) and whether the patient had LBBB or RBBB or another intra-ventricular conduction defect (check box). We used this information to divide the patients into two QRS duration categories (<120 and e 120 milliseconds) and three QRS morphology categories: no BBB, LBBB, RBBB or "other non-specific intra-ventricular conduction defect" (IVCD). The latter QRS morphology category was created by adding together patients with a checkbox completed for IVCD and patients with a QRS duration e 120 milliseconds but neither LBBB nor RBBB reported on the case report form. Patients with a pacemaker (conventional or a resynchronization device) were excluded in the present analysis, as were patients with implausible QRS widths (<60 and >220 milliseconds).

Clinical outcomes: The clinical outcomes of interest in this analysis were the composite outcome of cardiovascular death or heart failure hospitalization and its components, as these are thought to best reflect disease-specific outcomes.

Statistical analyses: Baseline characteristics were summarized as mean with standard deviation for continuous variables and numbers with percentages for categorical variables. Baseline characteristics were compared between the QRS duration categories using student's t test for continuous variables and the chi-square test for categorical variables. Baseline characteristics across QRS morphology categories were compared using ANOVA for continuous variables and chi-square test for categorical variables. Duration of heart failure, Minnesota living with heart failure questionnaire (MLHFQ) scores and N-terminal pro B-type natriuretic peptide (NT pro-BNP) were not normally distributed and therefore were summarized as medians and interquartile ranges and analyzed using the Mann-Whitney U test or Kruskal-Wallis test. Event rates for each of the outcomes of interest in each of the QRS duration and morphology categories were calculated per 100 patient years of follow-up and also illustrated using Kaplan-Meier curves and compared with the log rank test. The hazard ratios (HR) were calculated using Cox proportional hazard models adjusting for the prognostic variables identified to be most predictive of outcomes, as previously reported.[12] These variables included age, left ventricular ejection fraction, heart rate, ischemic aetiology, diabetes mellitus, myocardial infarction, hospitalization for heart failure in the past 6 months, history of chronic obstructive pulmonary disease or asthma, neutrophil count, estimated glomerular filtration rate, and NT pro-BNP. [12] A total of 663 patients with missing data (mainly NT pro-BNP) were excluded from the multivariable analyses. All P-values are two-sided and a value of <0.05 was considered significant. All statistical analyses were performed using Stata version 12 (Stata Corp, College Station, TX, USA). A variety of sensitivity analyses were conducted including examination of different QRS duration categories (QRS duration dichotomized at 130 milliseconds; QRS duration categories <120, 120-149, e 150 milliseconds), different QRS morphologies (RBBB,

LBBB and IVCD separately), and QRS duration as a continuous variable. QRS duration and morphology were also added simultaneously to the multivariable model and we tested for a possible interaction between QRS duration/morphology and atrial fibrillation at baseline.

RESULTS

A total of 4128 patients were randomized in I-Preserve. Of these, 252 had a pacemaker and were therefore excluded from analysis. A further 11 patients had a missing QRS duration or a QRS duration that was implausibly low (n=92) or high (n=19), leaving 3754 patients for analysis. Overall, QRS duration was <120 milliseconds in 3148 patients (84%) and e 120 milliseconds in 606 patients (16%). Of all analysable patients, investigators identified 302 (8.0%) as having LBBB, 261 (7.0%) with RBBB and 481 (12.8%) with non-specific intra-ventricular conduction defect (IVCD) i.e. 742 (19.8%) had non-LBBB QRS abnormalities. Seventy two percent of analysable patients (2710) had no abnormality of QRS configuration. The mean (standard deviation) QRS duration was 135 (25), 112 (27) and 86 (12) milliseconds in the LBBB, RBBB/IVCD and normal QRS morphology groups, respectively. Of the 606 patients with a QRS duration e 120 milliseconds, 249 (41.1%) had LBBB, 192 (31.7%) had RBBB and 165 (27.2%) had non-specific IVCD.

Baseline characteristics

Table 1a shows the baseline characteristics of patients according to QRS duration category and Table 1b according to QRS morphology category.

QRS duration: Compared to those with a QRS duration <120 milliseconds, patients with a longer QRS duration were slightly older on average, more commonly male, were more likely to have a history of myocardial infarction and had a lower mean left ventricular ejection fraction. Longer QRS duration was also associated with worse renal function and a higher mean NT pro-BNP level.

When compared to a QRS duration <120 milliseconds, those with a longer QRS duration were more likely to display certain adverse clinical signs such as ventricular gallop (S3) and jugular venous distension. Patients with a QRS duration e 120 milliseconds were less likely than those with a narrower QRS duration to have peripheral oedema but were more likely to be treated with a loop diuretic therapy and less likely to be treated with a calcium channel blocker. Baseline characteristics for patients dichotomized at a QRS duration of 130 milliseconds and categorized into three groups according to QRS duration <120, 120-149 and e 150 milliseconds are shown in the Supplementary Appendix (Tables 1-5).

QRS morphology: Compared to those with a normal QRS morphology, patients with abnormal QRS morphology showed similar patterns to those described above for patients with a QRS duration e 120 milliseconds and some additional differences including longer duration of heart failure and worse NYHA functional class. Those with abnormal QRS morphology had higher (worse) Minnesota Living With Heart Failure Questionnaire scores and generally, patients with LBBB had more manifestations of severe heart failure than those with RBBB/IVCD e.g. lower LVEF, worse NYHA class, higher NT pro-BNP, lower haemoglobin and worse renal function and greater diuretic use but did not have longer duration of heart failure or more frequent recent hospitalization for heart failure (although we cannot account for survivor bias). Baseline characteristics for patients categorized into four QRS morphology groups (normal, RBBB, LBBB and IVCD) are shown in the Supplementary Appendix (Tables 6 and 7).

Clinical outcomes

Rates of the composite outcome and its components (cardiovascular death and heart failure hospitalization), along with death from any cause are shown in Table 2. As can be seen from Table 2 (and Figures 1&2) both prolonged QRS duration and abnormal QRS morphology were associated

with a considerably higher risk of the composite outcome, compared with a QRS duration <120 milliseconds and normal QRS morphology separately.

QRS duration: In patients with a QRS duration <120 milliseconds, the rate of the composite outcome was 6.0 per 100 patient years of follow-up whereas in those with a prolonged QRS duration the rate was approximately 9.3 per 100 patient years of follow-up (Table 2). On univariate analysis, the risk of the composite outcome was 50% higher among patients with a prolonged QRS duration and the hazard was only slightly attenuated (to 32% higher) after adjustment in the multivariable model including NT pro-BNP (and this did not change significantly after further adjustment for male sex and baseline treatment with a loop diuretic). A similar pattern was seen for both components of the composite although the hazard ratio for cardiovascular death was higher than for heart failure hospitalization. Longer QRS duration was associated with a higher risk of the two main modes of cardiovascular death i.e. sudden death and pump failure death and the elevation in risk of each type of death was proportionately similar. The risk of death from any cause was also higher in patients with a QRS duration e 120 milliseconds compared to those with a QRS duration <120 milliseconds (Table 2). Qualitatively similar findings were seen dichotomizing QRS duration at 130 milliseconds (Supplementary Appendix Table 2; Figures 1-4). The elevated risk associated with longer QRS duration was not greater in patients with a QRS duration e150 milliseconds compared with a duration of 120-149 milliseconds (Supplementary Appendix Table 4; Figures 5-8). When QRS duration was examined as a continuous variable, a linear relationship was observed for cardiovascular (and all-cause) death up to a QRS duration of approximately 130 milliseconds (Supplementary Appendix Table 5).

QRS morphology: In patients with normal QRS morphology, the rate of the primary composite outcome was 6.0 per 100 patient years of follow-up whereas in those with RBBB/IVCD it was 7.7 per 100 patient years of follow-up and in individuals with LBBB it was 8.7 per 100 patient years of

follow-up (Table 2). On univariate analysis, the risk of the composite outcome was 30% higher among patients with RBBB/IVCD and 40% higher among those with LBBB. The hazard was somewhat attenuated after adjustment in the multivariable model - to 19% and 31%, respectively (and this did not change significantly after further adjustment for male sex and baseline treatment with a loop diuretic). A similar pattern was seen for both components of the composite although the hazard ratio for cardiovascular death was higher than for heart failure hospitalization for both types of conduction disturbance. The hazard ratios for the composite and both its components were also higher in the LBBB group compared with the non-LBBB group. Similarly the risk of the two main modes of cardiovascular death was elevated more in patients with LBBB than in the non-LBBB group (but the elevation in risk of each type of death was proportionately similar). The risk of death from any cause was also higher in patients with an abnormal QRS morphology and higher in those with LBBB compared with RBBB/IVCD (Table 2). When patients were categorized into four QRS morphology groups, the adjusted hazard ratios, compared with a normal QRS, were numerically (but not statistically significantly) less elevated in the RBBB group than in the LBBB and IVCD groups (Supplementary Appendix Table 7; Figures 9-12).

QRS duration and morphology considered simultaneously: We also entered both QRS duration and QRS morphology into the multivariable model simultaneously. For the outcome of cardiovascular death, QRS morphology did not substantially diminish the predictive value of QRS duration (examined as a continuous variable) whereas simultaneous entry of QRS duration (continuous) largely eliminated the predictive value of QRS morphology for cardiovascular (and all-cause) mortality. The superior predictive value of QRS duration over QRS morphology, when both variables were modelled simultaneously, was not as clear for heart failure hospitalization (Supplementary Appendix Tables 8 and 9).

We found no interaction between QRS duration or QRS morphology and atrial fibrillation at baseline.

DISCUSSION

The main findings in this study were that among the HF-PEF patients enrolled in I-Preserve those with a prolonged QRS duration or BBB experienced a considerably higher risk of the composite outcome of cardiovascular death or heart failure hospitalization (particularly cardiovascular death), compared to patients without such ECG abnormalities.

A prolonged QRS duration is found in 24 to 47% of patients with HF-REF and is believed to be a surface marker of left ventricular mechanical dys-synchrony.[13-17] Patients with HF-REF and QRS prolongation, especially if associated with a LBBB pattern, have a guideline indication for cardiac resynchronization therapy.[5,6] Few studies however, have examined the prevalence of QRS prolongation or described QRS morphology in patients with chronic HF-PEF and fewer still have examined their impact on clinical outcomes.

We found that 16% of patients in I-Preserve had prolonged QRS duration. The only other sizeable study to describe the prevalence of ECG abnormalities in ambulatory patients with HF-PEF was the Swedish Heart Failure Registry which enrolled over 57 000 individuals between May 2000 and March 2011.[8] Of those with a preserved left ventricular ejection fraction (e 50%), a very similar proportion, 18%, had a prolonged QRS duration. However, this was a much lower proportion than in patients with HF-REF i.e. 39% of patients with an ejection fraction <40%.

We found that nearly 20% of patients in I-Preserve were reported to have RBBB/IVCD (7% RBBB and 13% IVCD) and an additional 8% had LBBB morphology. We are not aware of any prior report about the specific type of QRS configuration in a large cohort of ambulatory patients with

HF-PEF. However, in the CHARM Programme, 14.4% with HF-PEF had *undifferentiated* BBB, compared with 30.1% of those with HF-REF.[15] Other large studies in patients with HF-REF have also described a much larger proportion of patients with BBB compared with the proportion in I-Preserve. Additionally, those other studies describe a greater fraction of patients with LBBB and a smaller proportion with RBBB/IVCD. For example, the prevalence of LBBB was 25% in the large Italian Network on Congestive Heart Failure Registry, compared with the 8% we found in I-Preserve whereas the proportion of patients with RBBB/IVCD was 12% compared with 20% in I-Preserve.[10]

The prevalence of a wide QRS complex in I-Preserve was much higher than in the general population. For example, among close to 15,000 individuals without known coronary heart disease (CHD) in the Atherosclerosis Risk in Communities study ARIC, only 456 (3.1%) had a QRS duration e120ms.[18] Among 1759 subjects without CHD or heart failure in the Framingham Heart Study, 113 (6.4%) had a QRS duration e120ms.[19] In I-Preserve, this proportion was 16% - not nearly as common as in HF-REF but much more than in the general population, presumably reflecting greater co-morbidity and myocardial damage in the patients in I-Preserve.[20] We found that previous myocardial infarction and longer duration heart failure, both of which are likely to lead to myocardial fibrosis, were associated with QRS abnormalities. However, neither hypertension nor diabetes, which might also be expected to have similar pathophysiological effects, were more common in patients with QRS abnormalities. Other pathophysiological abnormalities such as microvascular disease and vascular rarefaction might also lead to myocardial ischaemia, necrosis and fibrosis.[21]

As mentioned earlier, QRS prolongation and BBB morphology are surface markers of left ventricular mechanical dys-synchrony in patients with HF-REF. A recent analysis of 130 HF-PEF

patients in the Prospective comparison of ARNI (Angiotensin receptor neprilysin inhibitor) with ARB (Angiotensin receptor blocker) on management of heart failure with preserved ejection fraction trial (PARAMOUNT) found that 13% had evidence of mechanical dys-synchrony on 2D speckle tracking echocardiographic analysis, and this correlated with QRS prolongation on the surface ECG.[9] It is therefore possible that the substantial minority of patients with QRS abnormalities in I-Preserve had underlying mechanical dys-synchrony. Certainly, the I-Preserve patients with abnormal QRS duration and morphology had evidence of more severe heart failure (lower LVEF, lower eGFR, higher NT proBNP) and worse clinical status (higher NYHA functional class, greater use of diuretics), consistent with the clinical picture in patients with HF-REF and QRS abnormalities.

We found that abnormal QRS duration and morphology were associated with worse clinical outcomes in patients with HF-PEF, including higher rates of death (cardiovascular death in particular) and hospitalization for worsening heart failure. This association with higher mortality and to a lesser extent, heart failure hospitalization, persisted after extensive adjustment for other prognostic variables, including NT pro-BNP. This finding is consistent with prior studies in HF-REF. We know of only one other large study examining outcomes according to QRS *duration* in ambulatory patients with HF-PEF. In the Swedish Heart Failure Registry, QRS prolongation was related to higher all-cause mortality although this association was stronger in patients with a lower LVEF.[8] We found that the association between QRS duration and cardiovascular mortality was stronger than for all-cause mortality in I-Preserve, probably because QRS abnormalities are not predictive of non-cardiovascular death and non-cardiovascular causes of death are relatively common in patients with HF-PEF, compared with HF-REF. Heart failure hospitalization was not reported in the Swedish Registry study but we found that QRS prolongation is also a predictor of this non-fatal outcome in HF-PEF although not as strong a predictor as for cardiovascular death.

We also showed that abnormal QRS *morphology* is associated with worse outcomes and that LBBB appeared to carry a greater risk than RBBB/IVCD. These findings contrast with those of the CHARM Programme where *undifferentiated* BBB was associated with significantly worse outcomes in HF-PEF in univariate analyses but not in the multivariable analyses. This difference may reflect the relatively small number of patients with BBB in CHARM-Preserved (n=434).[15]

When we examined the predictive value of QRS duration and morphology *simultaneously*, only QRS duration was predictive of cardiovascular (and all-cause) death. This observation is of interest given the recent meta-analysis demonstrating that the benefit of cardiac resynchronization therapy (CRT) in HF-REF was predicted by QRS duration more than QRS morphology (QRS morphology did not add any predictive information over and above QRS duration examined as a continuous variable). This meta-analysis also demonstrated that CRT was most clearly of benefit in patients with a QRS duration e 130 milliseconds.[22]

Although the elevated risk associated with abnormal QRS duration or morphology was modest (with the highest adjusted hazard ratio for the primary composite outcome of 1.32 for a QRS duration of e 120ms), this is a larger increment in risk than associated with a 5 year increase in age or prior myocardial infarction and similar to that related to diabetes.

As with any analysis of this type there are limitations. It was not prospectively planned i.e. was retrospective. This, plus the examination of 5 subgroups and 4 endpoints increases the risk of chance findings. Original ECGs were not available and this analysis was based on information provided by investigators on study case report forms.

In summary, we found that HF-PEF patients with prolonged QRS duration or BBB experienced a considerably higher risk of the primary composite outcome of cardiovascular death or heart failure

hospitalization, compared to patients without these ECG abnormalities. Despite advances in technology, the ECG remains an accessible tool for identifying heart failure patients with ventricular conduction delay who are at high cardiovascular risk, regardless of whether they have reduced or preserved ejection fraction.

CLINICAL PERSPECTIVES

Our findings have a number of clinical implications. Firstly, it seems clear that QRS abnormalities are independent and important prognostic variables in HF-PEF - which may be useful in risk stratification clinically and in decisions about intensity of patient surveillance and follow-up. As little is known about the incidence of QRS prolongation/BBB in HF-PEF, future studies may also look at the development of new QRS abnormalities and the significance of this. QRS abnormalities may also provide a means of selecting higher-risk patients for clinical trials. Lastly, and more controversially, the current findings also raise the possibility that cardiac resynchronization therapy might have a therapeutic role in HF-PEF, as in HF-REF.[7, 17, 22,23] CRT has been shown to be ineffective or even harmful in patients with HF-REF who do not have "electrical dys-synchrony" (i.e. an abnormal) QRS as opposed to mechanical dys-synchrony.[24] This intervention however, has recently been tested in a small trial involving 24 participants with HF-PEF, normal QRS duration on electrocardiography and features of mechanical dys-synchrony on echocardiography. The results showed signs of improved ventricular relaxation accompanied by a small but significant improvement in diastolic and systolic haemodynamics at longer atrio-ventricular pacing intervals during biventricular, or isolated left ventricular pacing.[25] It is therefore possible that CRT might be beneficial in patients with interventricular dys-synchrony as demonstrated by QRS prolongation.[7] Clearly, however, this hypothesis would need to be tested in a randomized clinical trial. Identification of HF-PEF patients potentially suitable for device therapy might be one approach to targeting treatment to a particular HF-PEF phenotype. We recently published a study using latent class analysis to try and identify specific HF-PEF phenotypes in I-Preserve and validated this approach in CHARM-Preserved. Unfortunately, because CHARM did not collect information on QRS duration and morphology, QRS variables were not included in the latent class analysis.[26]

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Table legends

Table 1a. Baseline Characteristics according to QRS duration

Table 1b. Baseline Characteristics according to QRS morphology category

Table 2. Endpoints according to QRS duration and morphology category

Figure legends

Figure 1: Cardiovascular death or hospitalization for HF according to QRS duration

Figure 2: Cardiovascular death or hospitalization for HF according to QRS morphology

Table 1a. Baseline Characteristics according to QRS duration

Characteristic	QRS duration - msec <120 (N=3148)	QRS duration - msec ≥120 (N=606)	p-value
Age - year	71.2 ± 6.8	72.5 ± 6.9	<0.0001
Male sex - no.(%)	1174 (37.3)	302 (49.8)	<0.0001
Race - no.(%)			0.53
White	2947 (93.6)	575 (94.9)	
Black	65 (2.1)	11 (1.8)	
Asian-Pacific	17 (0.5)	4 (0.7)	
Other	119 (3.8)	16 (2.6)	
Body-mass index	29.7 ± 5.2	29.7 ± 5.5	0.93
Heart rate - beats/min	71.5 ± 10.6	71.3 ± 10.3	0.61
Blood Pressure - mmHg			
Systolic	136.6 ± 14.7	136.7 ± 15.1	0.90
Diastolic	79.1 ± 8.9	78.5 ± 9.4	0.10
Ejection fraction - %	59.7 ± 9.0	57.6 ± 9.1	<0.0001
NYHA class - no.(%)			0.72
II	661 (21.0)	130 (21.5)	
III	2404 (76.4)	456 (75.4)	
IV	82 (2.6)	19 (3.1)	
Etiology - no.(%)			0.29
Ischemic	776 (24.7)	167 (27.6)	
Hypertension	2049 (65.1)	376 (62.0)	
Other	323 (10.3)	63 (10.4)	
Duration of heart failure - year			0.54
Median	1.1	1.0	
Q1,Q3	[0.2, 3.3]	[0.2, 3.6]	
Medical history - no.(%)			
Hospitalization for heart failure within previous 6 months	1376 (43.7)	266 (43.9)	0.93
Hypertension	2818 (89.5)	530 (87.5)	0.14
Stable angina	1291 (41.0)	225 (37.1)	0.07
Unstable angina	221 (7.0)	50 (8.3)	0.28
Myocardial infarction	718 (22.8)	164 (27.1)	0.02
PCI or CABG	382 (12.1)	88 (14.5)	0.10
Atrial fibrillation	874 (27.8)	156 (25.7)	0.31
Diabetes mellitus	842 (26.7)	169 (27.9)	0.56
Stroke or transient ischemic attack	288 (9.1)	66 (10.9)	0.18
COPD or asthma	274 (8.7)	64 (10.6)	0.14
Left bundle-branch block	53 (1.7)	249 (41.1)	<0.0001
Right bundle-branch block	69 (2.2)	192 (31.7)	<0.0001
IVCD	320 (10.2)	83 (13.7)	0.01
No BBB/IVCD	2710 (86.1)	0 (0.0)	<0.0001
MLHFQ Score†			0.17
Median	42.0	43.0	
Q1, Q3	[28.0, 59.0]	[27.0, 56.0]	
Symptoms and signs - no.(%)			

Ventricular gallop (S3)	234 (7.4)	71 (11.7)	0.0004
Jugular venous distention > 6 cm	248 (7.9)	63 (10.4)	0.04
Lungs			0.97
Basilar rales	777 (24.7)	151 (24.9)	
Diffuse rales	97 (3.1)	19 (3.1)	
wheeze	73 (2.3)	16 (2.6)	
Hepatomegaly	601 (19.1)	108 (17.9)	0.46
Peripheral oedema			0.004
none	1397 (44.4)	288 (47.5)	
trace	1024 (32.5)	162 (26.7)	
1+ to 2+	671 (21.3)	136 (22.4)	
3+ to 4+	54 (1.7)	20 (3.3)	
Medication - no.(%)			
Diuretic	2612 (83.1)	519 (85.6)	0.12
Loop	1597 (50.8)	335 (55.3)	0.04
Thiazide	1268 (40.3)	207 (34.2)	0.005
Spironolactone	463 (14.7)	101 (16.7)	0.22
ACE inhibitor	783 (24.9)	172 (28.4)	0.07
Beta blocker	1897 (60.3)	340 (56.1)	0.05
Calcium channel blocker	1282 (40.8)	221 (36.5)	0.05
Digitalis	418 (13.3)	72 (11.9)	0.35
Antiarrhythmic drug	259 (8.2)	54 (8.9)	0.58
Aspirin	1748 (55.6)	345 (56.9)	0.54
Antiplatelet	1861 (59.2)	375 (61.9)	0.21
Antithrombotic	548 (17.4)	108 (17.8)	0.81
Lipid-lowering agent	928 (29.5)	219 (36.1)	0.001
Laboratory measurements			
Hemoglobin - g/dl	14.0 ± 1.5	14.1 ± 1.5	0.43
Potassium - mmol/l	4.5 ± 0.5	4.5 ± 0.5	0.99
Creatinine - mg/dl	0.98 ± 0.31	1.04 ± 0.33	<0.0001
eGFR - ml/min/1.73 m2	73.5 ± 22.3	71.2 ± 22.5	0.02
eGFR <60 ml/min/1.73 m2 - no.(%)	883 (28.7)	204 (34.4)	0.01
Neutrophil -10^3 cells/ul	4.5 ± 1.8	4.5 ± 1.6	0.88
NT-pro BNP - pg/ml			<0.0001
Median	305.0	425.0	
Q1, Q3	[123.0, 855.0]	[175.0, 1116.0]	

NYHA, New York heart association; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; ICD, implantable cardioverter defibrillator; COPD, chronic obstructive pulmonary disease; IVCD, intra-ventricular conduction defect ; BBB, bundle branch block; MLHFQ , Minnesota Living with Heart Failure Questionnaire; ACE, angiotensin converting enzyme; eGFR, estimated glomerular filtration rate; NT-pro BNP, N-terminal pro-B type natriuretic peptide.

† Possible scores range from 0 to 105, with lower scores indicating a better quality of life.

Table 1b. Baseline Characteristics according to QRS morphology category

Characteristic	QRS morphology Category			p-value
	Normal	non-LBBB	LBBB	
	n=2710	n=742	n=302	
Age - year	71.1 ± 6.8	71.8 ± 6.8	72.6 ± 6.9	<0.001
Male sex - no.(%)	987 (36.4)	375 (50.5)	114 (37.7)	<0.0001
Race - no.(%)				0.35
White	2534 (93.5)	699 (94.2)	289 (95.7)	
Black	60 (2.2)	12 (1.6)	4 (1.3)	
Asian-Pacific	12 (0.4)	7 (0.9)	2 (0.7)	
Other	104 (3.8)	24 (3.2)	7 (2.3)	
Body-mass index	29.7 ± 5.2	29.8 ± 5.5	29.1 ± 5.0	0.13
Heart rate - beats/min	71.6 ± 10.6	70.5 ± 10.2	72.9 ± 10.6	0.002
Blood Pressure - mmHg				
Systolic	136.4 ± 14.7	137.1 ± 14.8	137.3 ± 14.7	0.41
Diastolic	78.9 ± 9.0	79.4 ± 9.1	78.9 ± 8.9	0.32
Ejection fraction - %	59.9 ± 9.2	58.8 ± 8.7	56.0 ± 8.5	<0.0001
NYHA class - no.(%)				0.003
II	580 (21.4)	164 (22.1)	47 (15.6)	
III	2068 (76.3)	554 (74.7)	238 (79.1)	
IV	61 (2.3)	24 (3.2)	16 (5.3)	
Etiology - no.(%)				0.08
Ischemic	661 (24.4)	202 (27.2)	80 (26.5)	
Hypertension	1763 (65.1)	479 (64.6)	183 (60.6)	
Other	286 (10.6)	61 (8.2)	39 (12.9)	
Duration of heart failure - year				<0.0001
Median	1.0	1.4	1.2	
Q1,Q3	[0.2, 3.2]	[0.3, 3.6]	[0.3, 3.9]	
Medical history - no.(%)				
Hospitalization for heart failure within previous 6 months	1214 (44.8)	317 (42.7)	111 (36.8)	0.02
Hypertension	2410 (88.9)	674 (90.8)	264 (87.4)	0.20
Stable angina	1066 (39.3)	325 (43.8)	125 (41.4)	0.08
Unstable angina	191 (7.0)	53 (7.1)	27 (8.9)	0.48
Myocardial infarction	595 (22.0)	213 (28.7)	74 (24.5)	<0.001
PCI or CABG	339 (12.5)	104 (14.0)	27 (8.9)	0.08
Atrial fibrillation	770 (28.4)	191 (25.7)	69 (22.8)	0.06
Diabetes mellitus	734 (27.1)	194 (26.1)	83 (27.5)	0.86
Stroke or transient ischemic attack	249 (9.2)	77 (10.4)	28 (9.3)	0.61
COPD or asthma	245 (9.0)	73 (9.8)	20 (6.6)	0.26
QRS e 120 milliseconds	0 (0.0)	357 (48.1)	249 (82.5)	<0.0001
QRS duration - milliseconds	86.1 ± 12.1	111.5 ± 26.6	134.5 ±25.0	<0.0001
MLHFQ Score†				0.004
Median	42.5	40.0	47.0	
Q1, Q3	[28.0, 59.5]	[27.0, 55.0]	[31.0, 60.0]	

Symptoms and signs - no.(%)				
Ventricular gallop (S3)	203 (7.5)	56 (7.5)	46 (15.3)	<0.0001
Jugular venous distention > 6 cm	212 (7.8)	72 (9.7)	27 (9.0)	0.23
Lungs				0.69
Basilar rales	664 (24.5)	182 (24.5)	82 (27.2)	
Diffuse rales	78 (2.9)	26 (3.5)	12 (4.0)	
Wheeze	61 (2.3)	21 (2.8)	7 (2.3)	
Hepatomegaly	482 (17.8)	155 (20.9)	72 (23.9)	0.01
Peripheral oedema				0.05
None	1250 (46.1)	301 (40.6)	134 (44.5)	
Trace	856 (31.6)	242 (32.6)	88 (29.2)	
1+ to 2+	557 (20.6)	179 (24.1)	71 (23.6)	
3+ to 4+	46 (1.7)	20 (2.7)	8 (2.7)	
Medication - no.(%)				
Diuretic	2241 (82.8)	625 (84.2)	265 (87.7)	0.07
Loop	1387 (51.2)	381 (51.3)	164 (54.3)	0.60
Thiazide	1037 (38.3)	320 (43.1)	118 (39.1)	0.06
Spironolactone	400 (14.8)	109 (14.7)	55 (18.2)	0.27
ACE inhibitor	680 (25.1)	190 (25.6)	85 (28.1)	0.52
Beta blocker	1641 (60.6)	437 (58.9)	159 (52.6)	0.02
Calcium channel blocker	1118 (41.3)	286 (38.5)	99 (32.8)	0.01
Digitalis	364 (13.4)	92 (12.4)	34 (11.3)	0.47
Antiarrhythmic drug	220 (8.1)	67 (9.0)	26 (8.6)	0.72
Aspirin	1500 (55.4)	419 (56.5)	174 (57.6)	0.70
Antiplatelet	1590 (58.7)	458 (61.7)	188 (62.3)	0.21
Antithrombotic	493 (18.2)	116 (15.6)	47 (15.6)	0.17
Lipid-lowering agent	838 (31.0)	210 (28.3)	99 (32.8)	0.26
Laboratory measurements				
Hemoglobin - g/dl	14.0 ± 1.5	14.2 ± 1.5	13.9 ± 1.4	0.001
Potassium - mmol/l	4.5 ± 0.5	4.4 ± 0.5	4.5 ± 0.5	0.86
Creatinine - mg/dl	0.98 ± 0.31	1.03 ± 0.33	0.99 ± 0.33	0.002
eGFR - ml/min/1.73 m2	73.3 ± 22.2	72.3 ± 22.6	73.3 ± 22.8	0.59
eGFR <60 ml/min/1.73 m2 -no.(%)	767 (29.0)	225 (31.0)	95 (31.6)	0.42
Neutrophil -10^3 cells/ul	4.5 ± 1.8	4.5 ± 1.6	4.5 ±1.5	0.78
NT-proBNP - pg/ml				0.003
Median	309.0	331.5	427.0	
Q1,Q3	[125.0, 878.0]	[130.5, 904.0]	[169.0, 1111.0]	

BBB, bundle branch block; LBBB, left bundle branch block; NYHA, New York heart association; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; ICD, implantable cardioverter defibrillator; COPD, chronic obstructive pulmonary disease; MLHFQ , Minnesota Living with Heart Failure Questionnaire; ACE, angiotensin converting enzyme; eGFR, estimated glomerular filtration rate; NT-pro BNP, N-terminal pro-B type natriuretic peptide.

† Possible scores range from 0 to 105, with lower scores indicating a better quality of life.

Table 2. Endpoints according to QRS interval and QRS morphology category

Endpoints	Event no. (%)	Rate (Per 100 patient years)	Hazard ratio	p value	Adjusted† hazard ratio	p value
CV death or HF hospitalisation						
QRS interval, msec						
<120	721 (22.9)	6.0 (5.6-6.5)	1.00		1.00	
≥120	200 (33.0)	9.3 (8.1-10.7)	1.54 (1.32-1.80)	<0.001	1.32 (1.11-1.57)	0.002
QRS morphology category						
Normal	616 (22.8)	6.0 (5.5-6.5)	1.00		1.00	
Non-LBBB	210 (28.3)	7.7 (6.7-8.8)	1.28 (1.10-1.50)	0.002	1.19 (1.00-1.42)	0.046
LBBB	94 (31.1)	8.7 (7.1-10.6)	1.44 (1.16-1.78)	0.001	1.31 (1.03-1.66)	0.026
HF hospitalisation						
QRS interval, msec						
<120	449 (14.3)	3.7 (3.4-4.1)	1.00		1.00	
≥120	117 (19.3)	5.5 (4.6-6.6)	1.44 (1.17-1.76)	0.001	1.24 (0.98-1.55)	0.069
QRS morphology category						
Normal	381 (14.1)	3.7 (3.3-4.1)	1.00		1.00	
Non-LBBB	127 (17.1)	4.7 (3.9-5.5)	1.25 (1.02-1.53)	0.029	1.14 (0.91-1.43)	0.267
LBBB	58 (19.2)	5.4 (4.1-6.9)	1.42 (1.08-1.88)	0.012	1.31 (0.96-1.77)	0.085
CV death						
QRS interval, msec						
<120	416 (13.2)	3.2 (2.9-3.5)	1.00		1.00	
≥120	128 (21.1)	5.4 (4.5-6.4)	1.68 (1.38-2.04)	<0.001	1.38 (1.11-1.72)	0.004
QRS morphology category						
Normal	354 (13.1)	3.2 (2.9-3.5)	1.00		1.00	
Non-LBBB	127 (17.1)	4.2 (3.6-5.0)	1.33 (1.09-1.63)	0.006	1.26 (1.00-1.57)	0.047
LBBB	63 (20.9)	5.3 (4.1-6.7)	1.66 (1.27-2.17)	<0.001	1.44 (1.08-1.93)	0.012
Sudden death						
QRS interval, msec						
<120	153 (4.9)	1.2 (1.0-1.4)	1.00		1.00	
≥120	53 (8.8)	2.2 (1.7-2.9)	1.89 (1.38-2.58)	<0.001	1.43 (1.01-2.02)	0.046
QRS morphology category						
Normal	129 (4.8)	1.2 (1.0-1.4)	1.00		1.00	
Non-LBBB	48 (6.5)	1.6 (1.2-2.1)	1.38 (0.99-1.93)	0.055	1.19 (0.82-1.72)	0.360

LBBB	29 (9.6)	2.4 (1.7-3.5)	2.09 (1.40-3.13)	<0.001	1.82 (1.18-2.80)	0.006
Pump failure death						
QRS interval, msec						
<120	78 (2.5)	0.6 (0.5-0.8)	1.00		1.00	
e120	27 (4.5)	1.1 (0.8-1.7)	1.89 (1.22-2.92)	0.004	1.56 (0.95-2.54)	0.78
QRS morphology category						
Normal	62 (2.3)	0.6 (0.4-0.7)	1.00		1.00	
Non-LBBB	27 (3.6)	0.9 (0.6-1.3)	1.62 (1.03-2.55)	0.037	1.46 (0.87-2.46)	0.155
LBBB	16 (5.3)	1.3 (0.8-2.2)	2.41 (1.39-4.17)	0.002	2.23 (1.24-4.01)	0.007
All cause death						
QRS interval, msec						
<120	618 (19.6)	4.8 (4.4-5.2)	1.00		1.00	
e120	162 (26.7)	6.8 (5.8-8.0)	1.43 (1.20-1.70)	<0.001	1.20 (0.99-1.45)	0.06
QRS morphology category						
Normal	532 (19.6)	4.8 (4.4-5.2)	1.00		1.00	
Non-LBBB	172 (23.2)	5.7 (4.9-6.7)	1.20 (1.01-1.43)	0.036	1.15 (0.95-1.39)	0.143
LBBB	76 (25.2)	6.4 (5.1-8.0)	1.33 (1.05-1.69)	0.019	1.15 (0.88-1.49)	0.303

† Adjusted for age, left ventricular ejection fraction, heart rate, ischemic aetiology, diabetes mellitus, myocardial infarction, hospitalization for heart failure in the past 6 months, history of chronic obstructive pulmonary disease or asthma, neutrophils, estimated glomerular filtration rate, and N-terminal pro-B type natriuretic peptide. 3091 patients without missing data were included in the adjusted model. CV, cardiovascular; HF, heart failure; BBB, bundle branch block; LBBB, left bundle branch block.

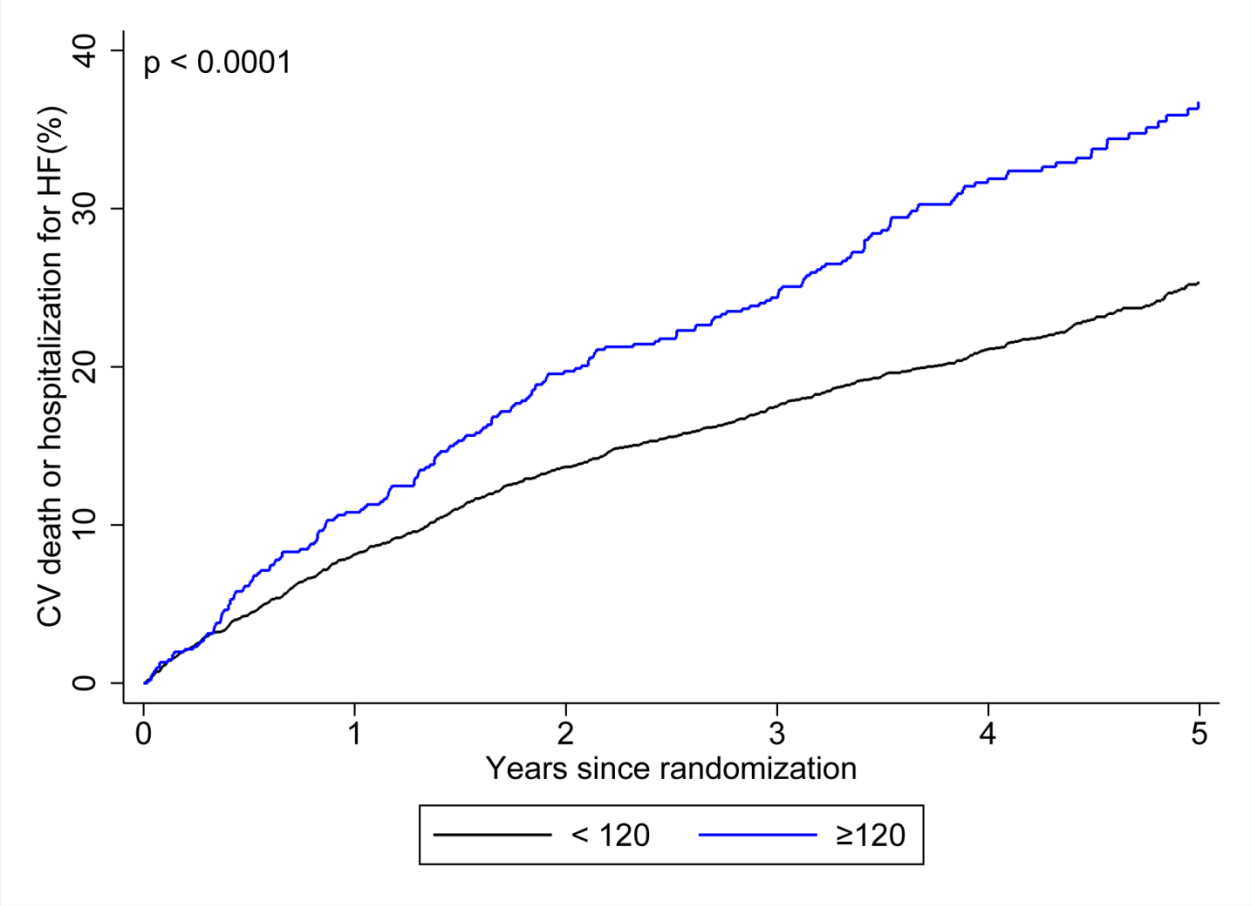

Figure 1: Cardiovascular death or hospitalization for HF according to QRS duration.
(A) QRS <120ms; (B) QRS ≥120ms

QRS morphology

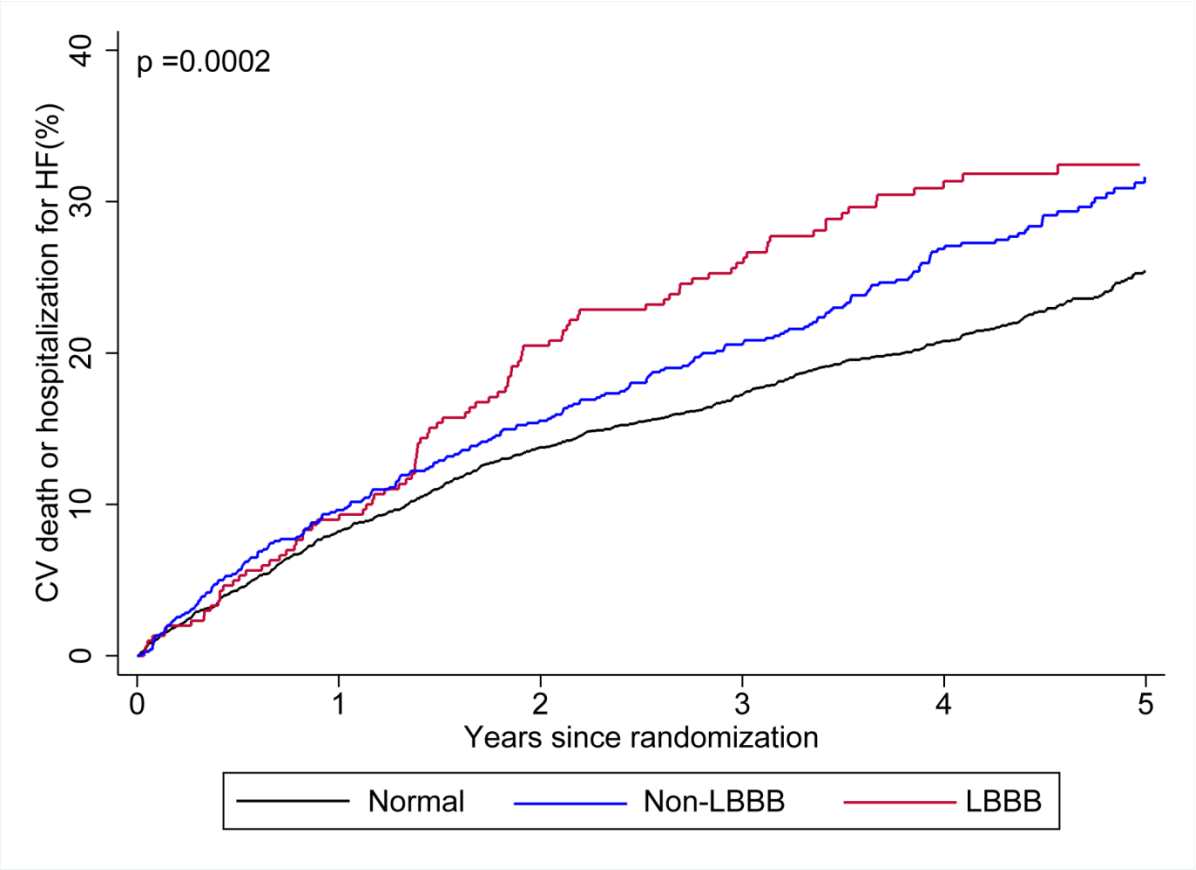

Figure 2: Cardiovascular death or hospitalization for HF according to QRS morphology. (A) Normal morphology; (B) Non-LBBB morphology (RBBB/IVCD); (C) LBBB morphology

Figure 1. Kaplan-Meier curve of the composite outcome according to QRS interval (130 msec as the cut-off)

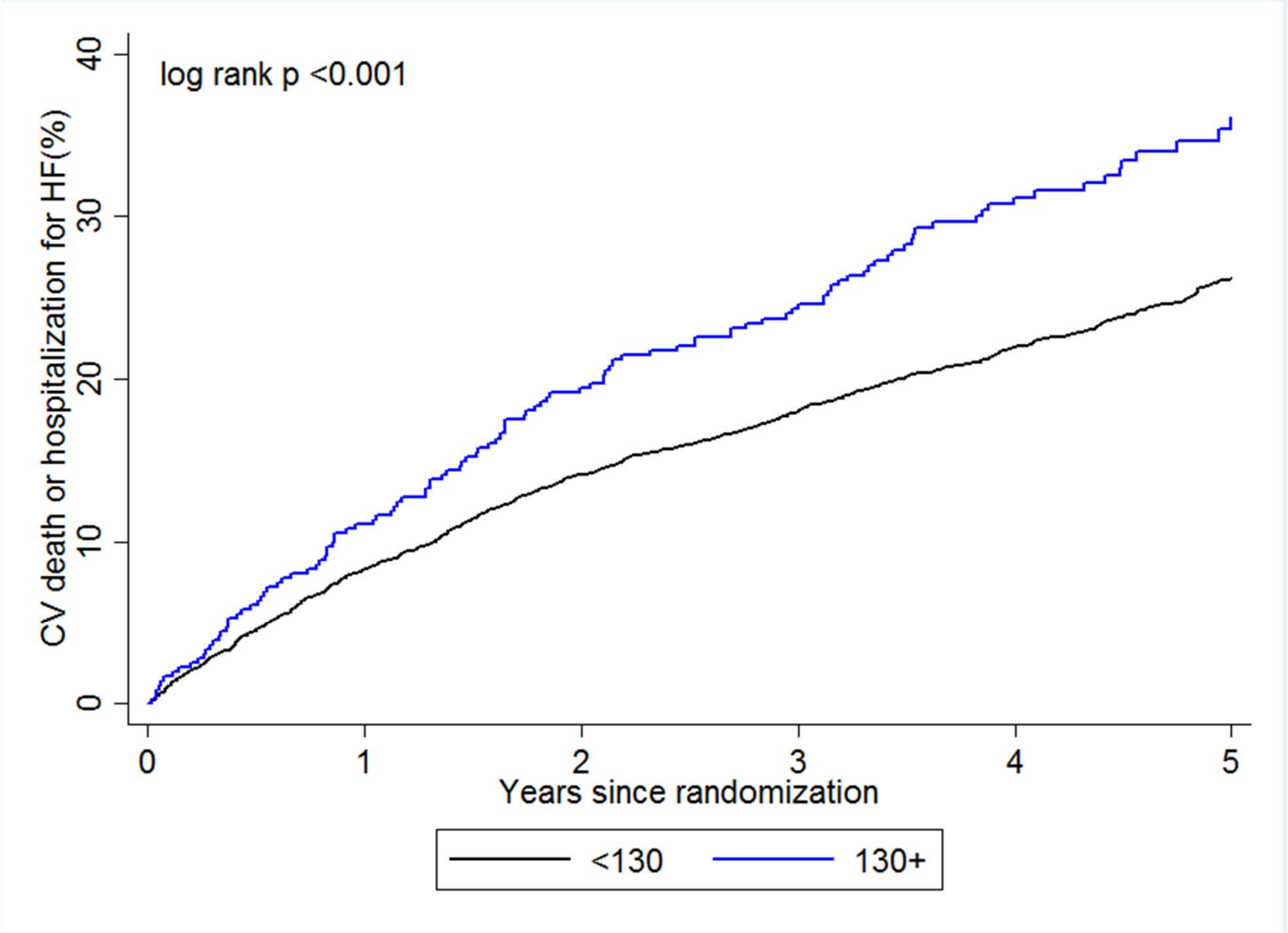

Figure 2. Kaplan-Meier curve of HF hospitalization according to QRS interval (130 msec as the cut-off)

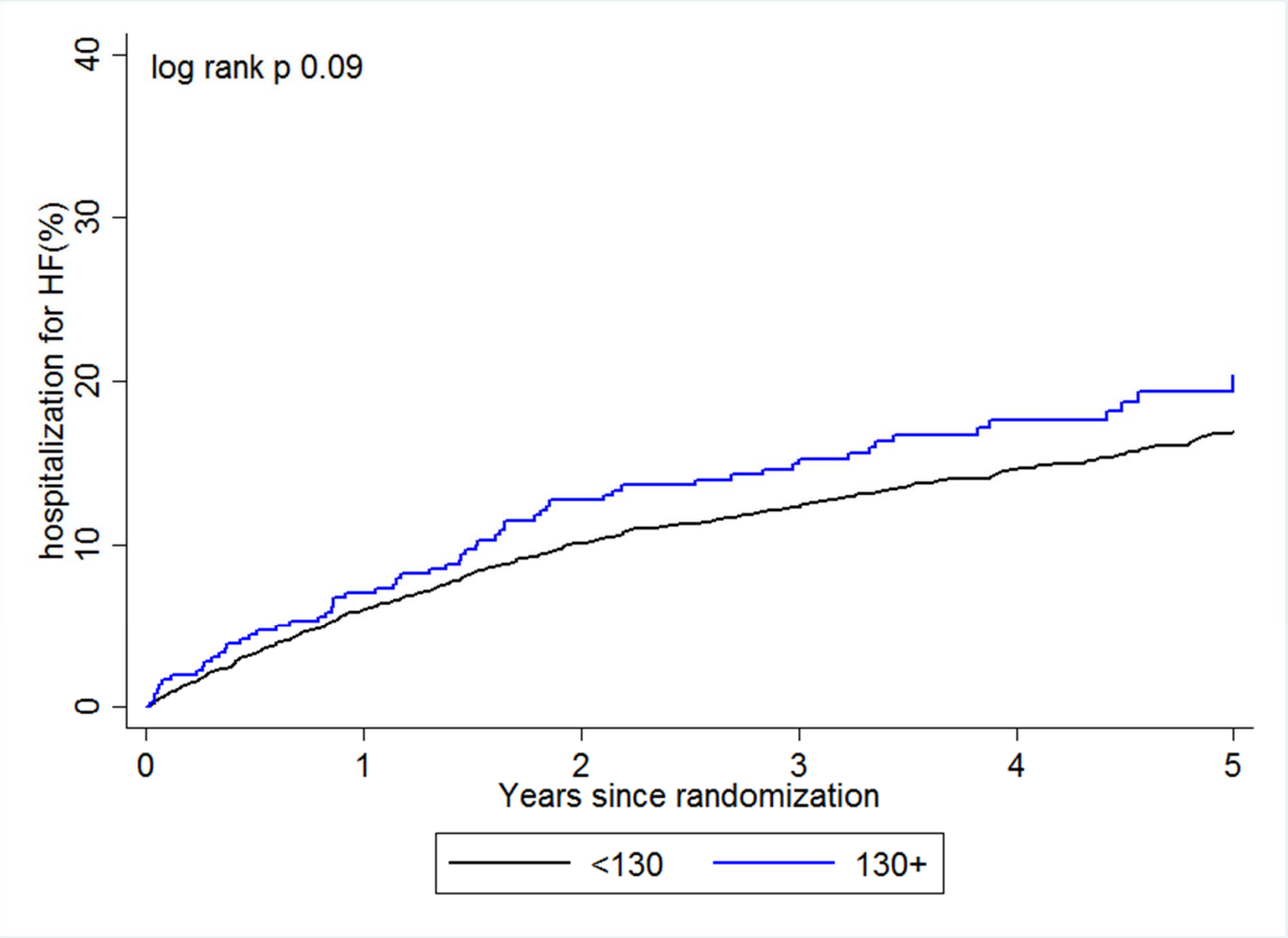

Figure 3. Kaplan-Meier curve of CV death according to QRS interval (130 msec as the cut-off)

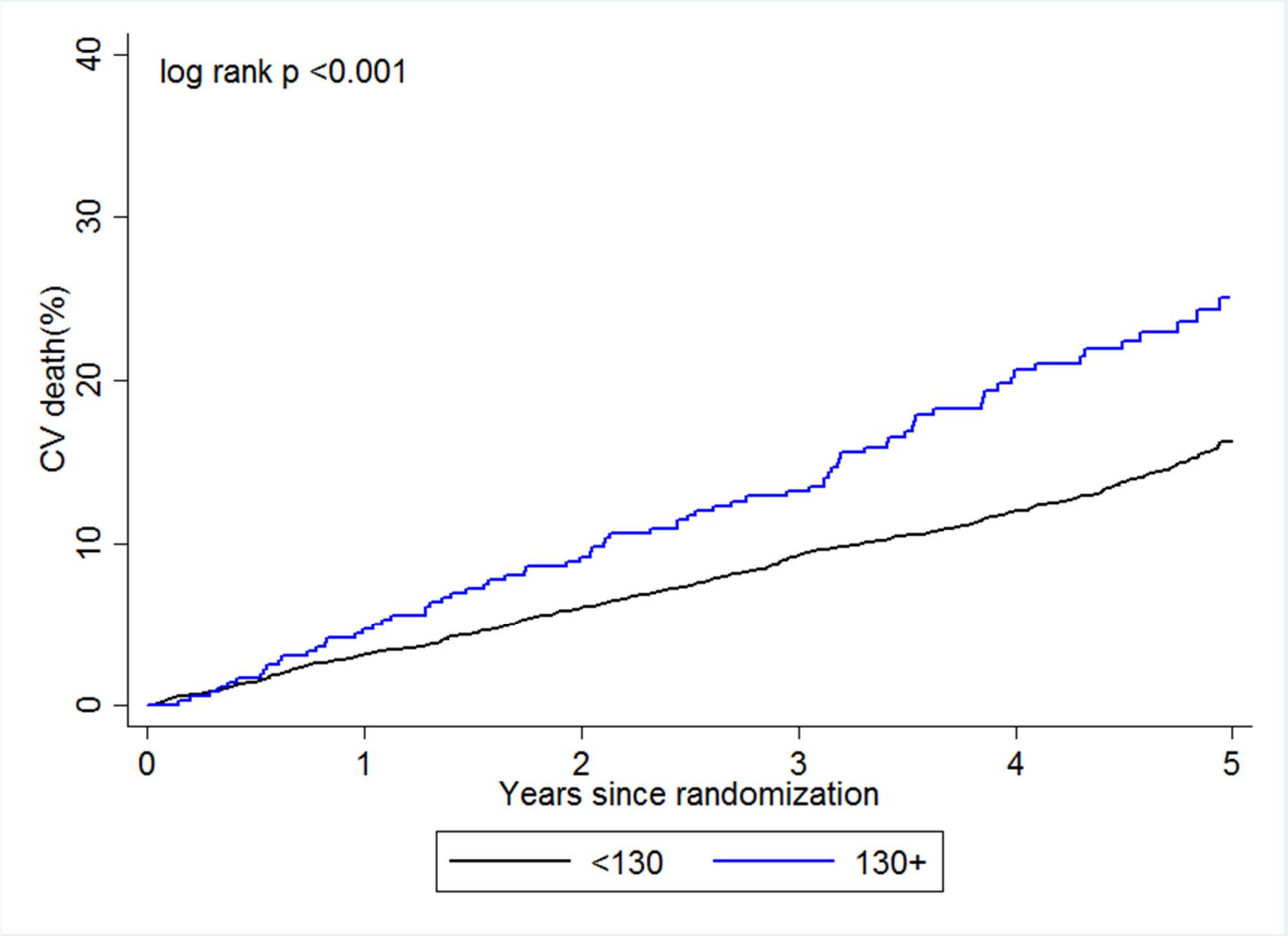

Figure 4. Kaplan-Meier curve of all-cause death according to QRS interval (130 msec as the cut-off)

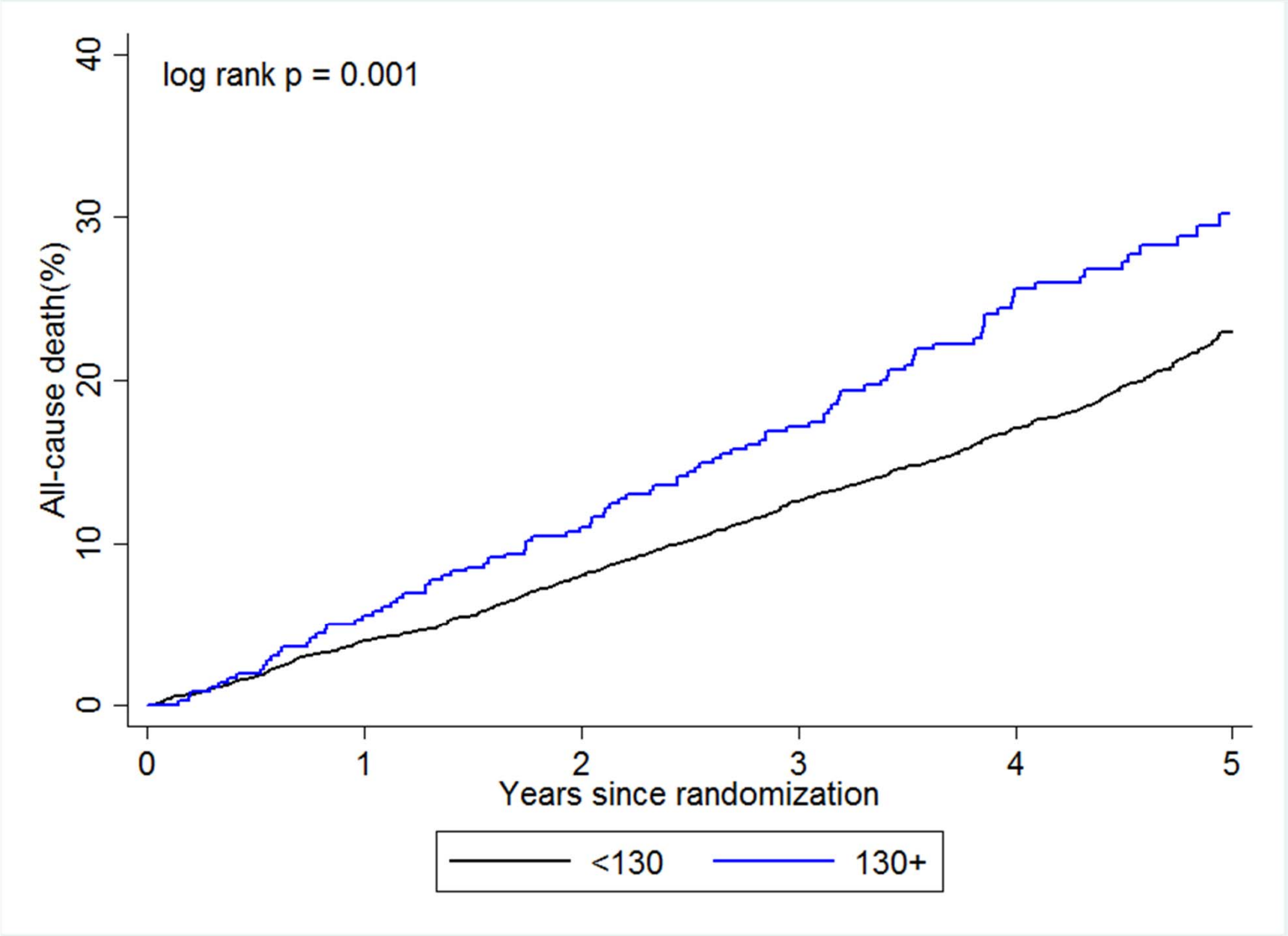

Figure 5. Kaplan-Meier curve of the composite outcome according to QRS interval (3 subgruops)

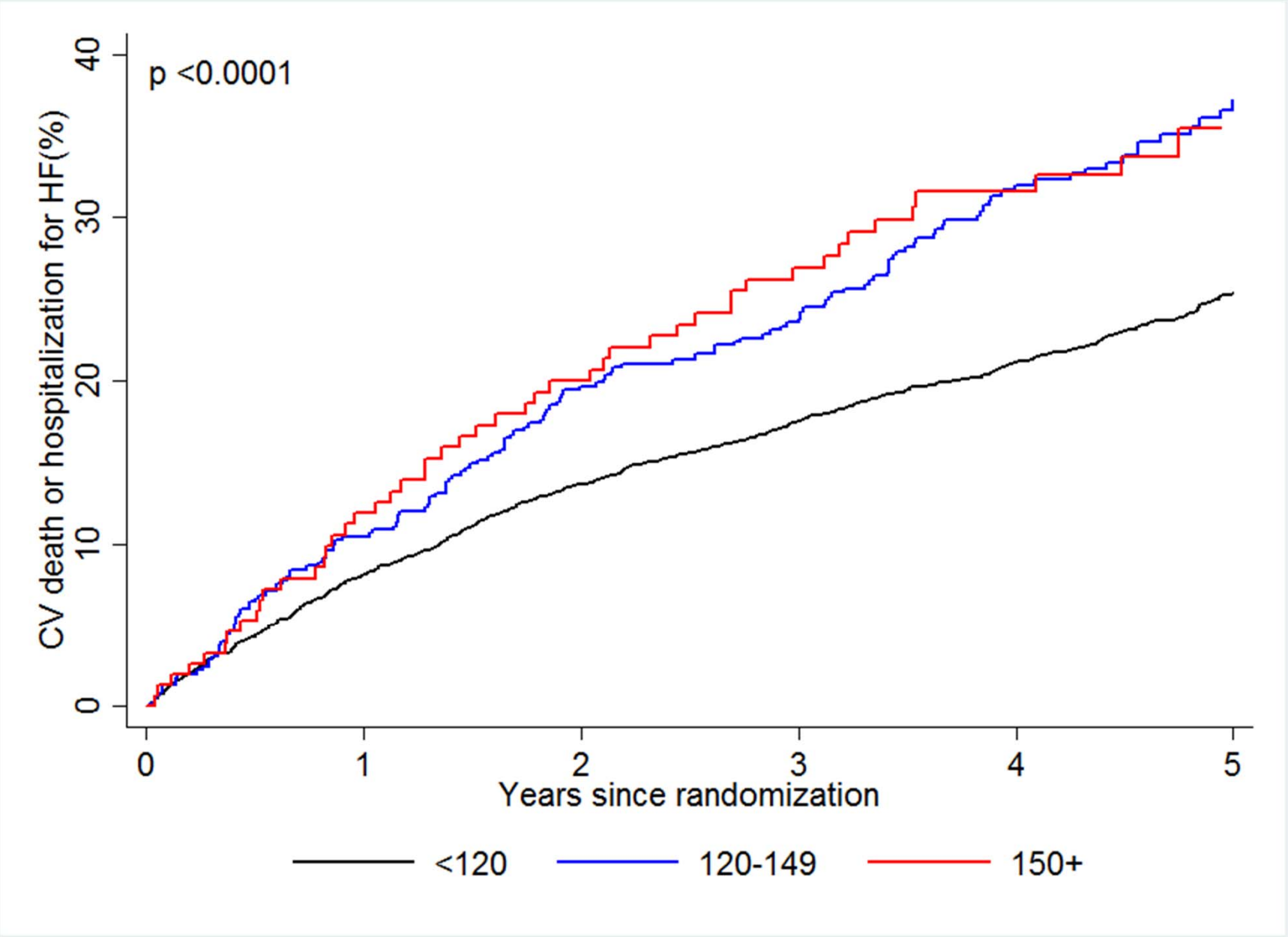

Figure 6. Kaplan-Meier curve of HF hospitalization according to QRS interval (3 subgruops)

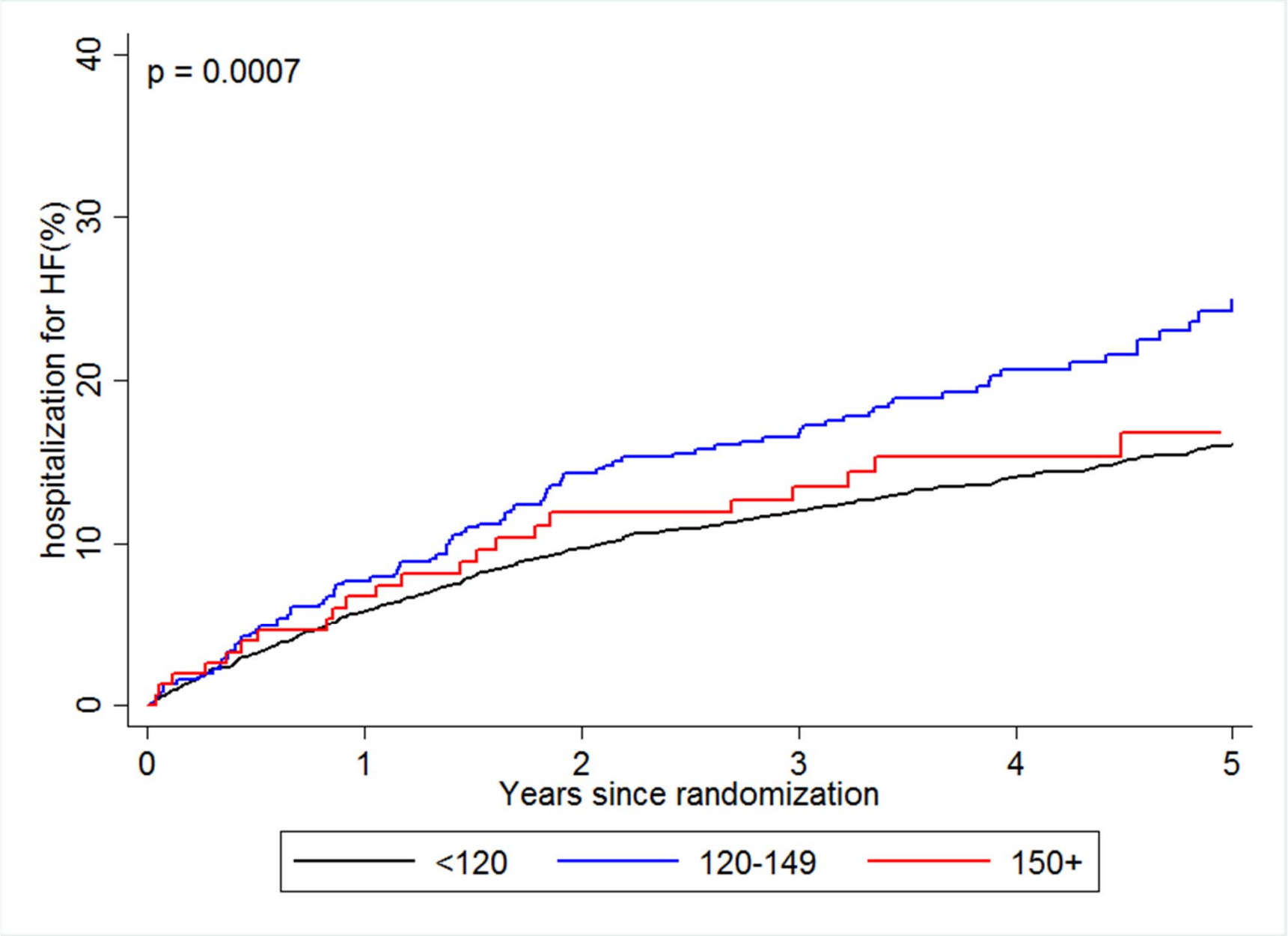

Figure 7. Kaplan-Meier curve of CV death according to QRS interval (3 subgruops)

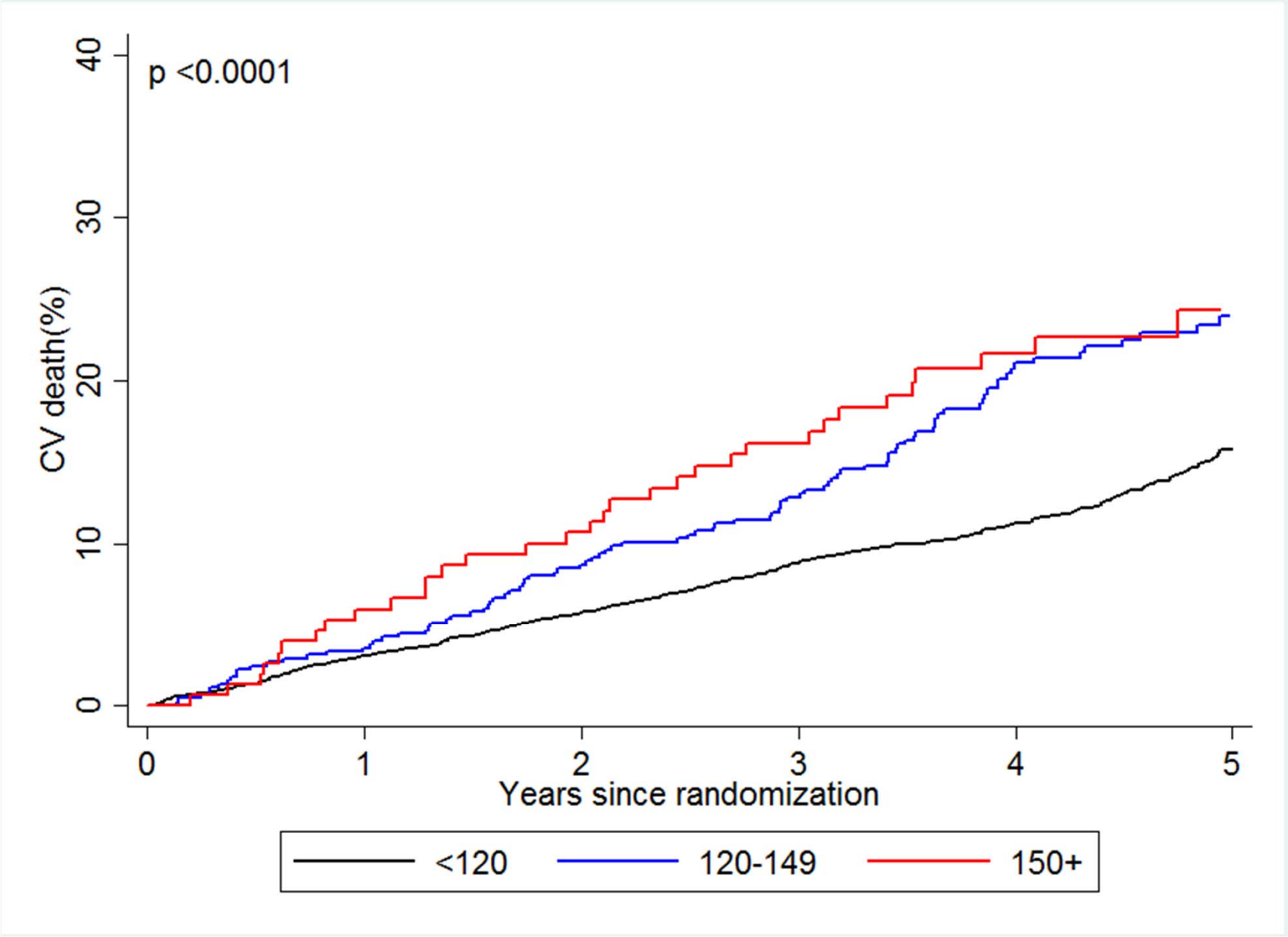

Figure 8. Kaplan-Meier curve of all-cause death according to QRS interval (3 subgruops)

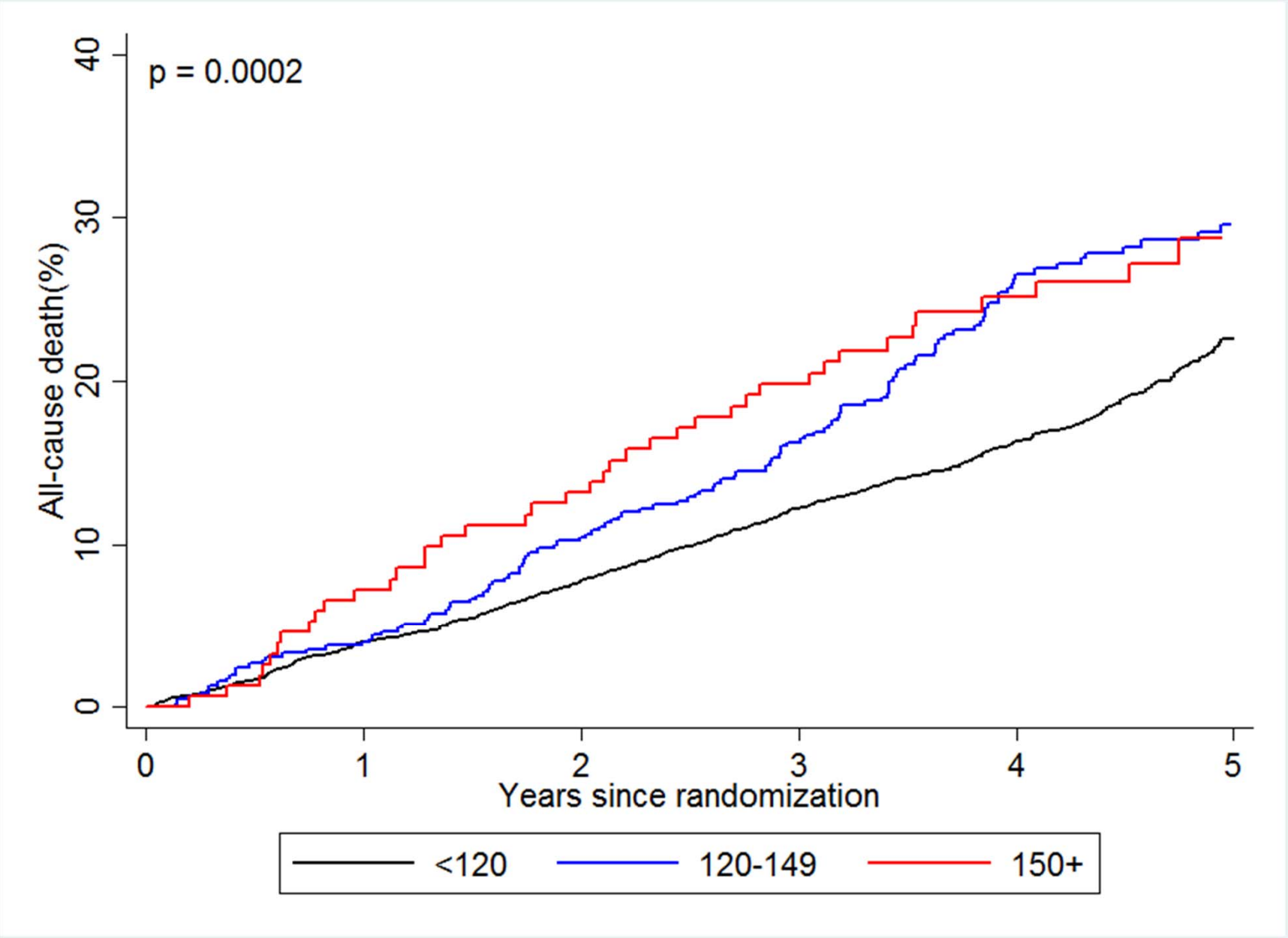

Figure 9. Kaplan-Meier curve of the composite outcome according to QRS morphology category (4 subgroups)

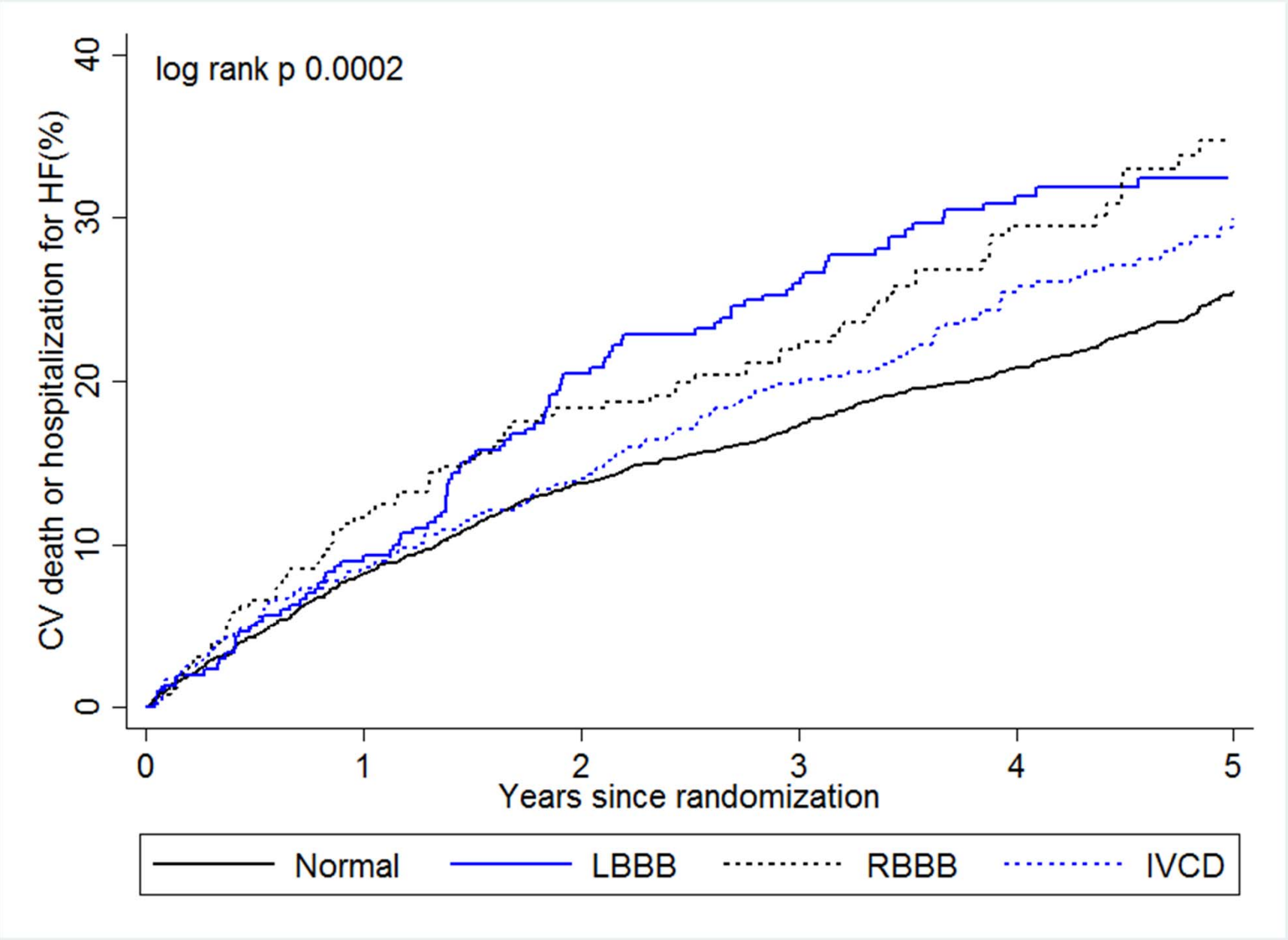

Figure 10. Kaplan-Meier curve of HF hospitalization according to QRS morphology category (4 subgroups)

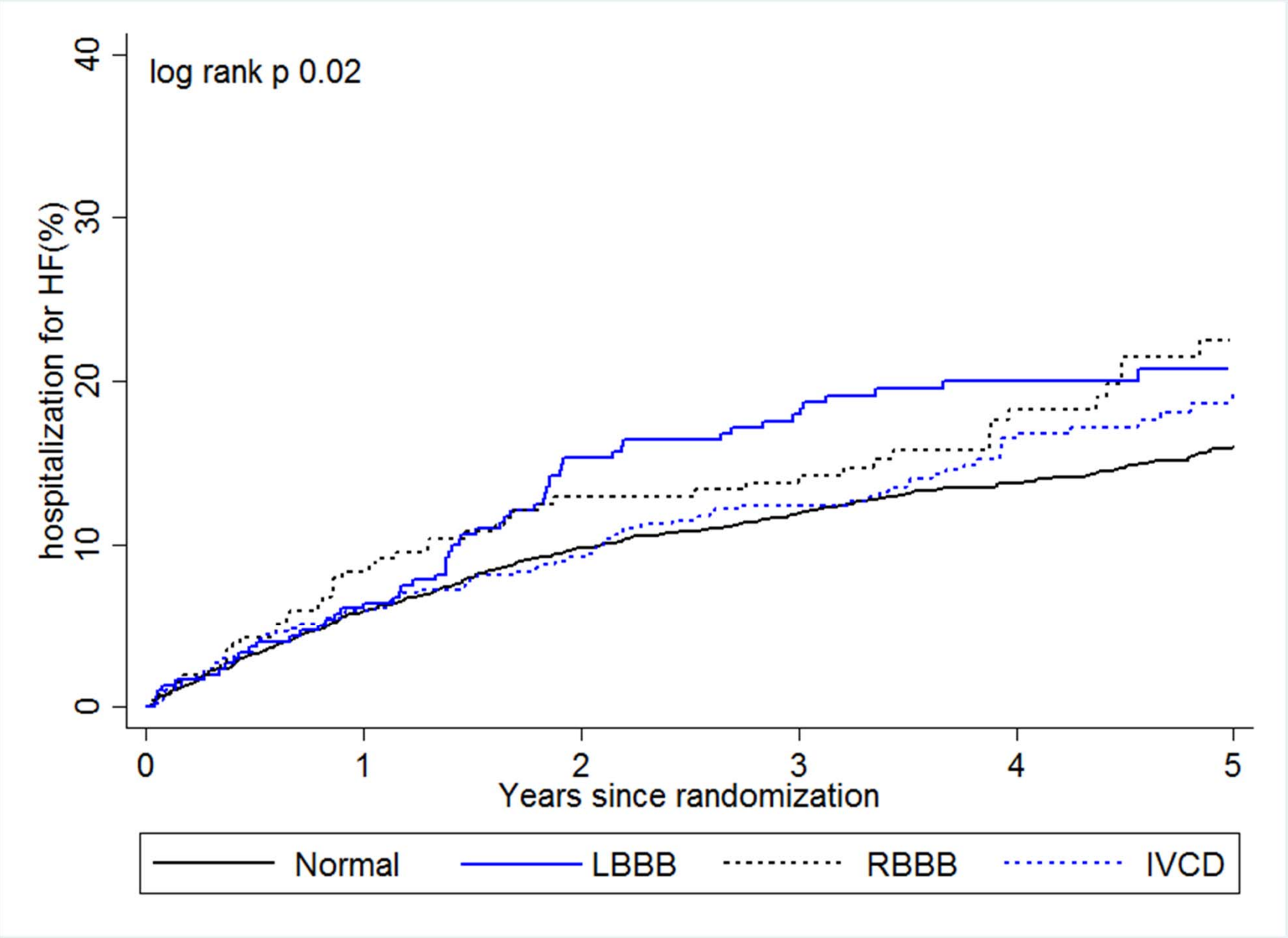

Figure 11. Kaplan-Meier curve of CV death according to QRS morphology category (4 subgroups)

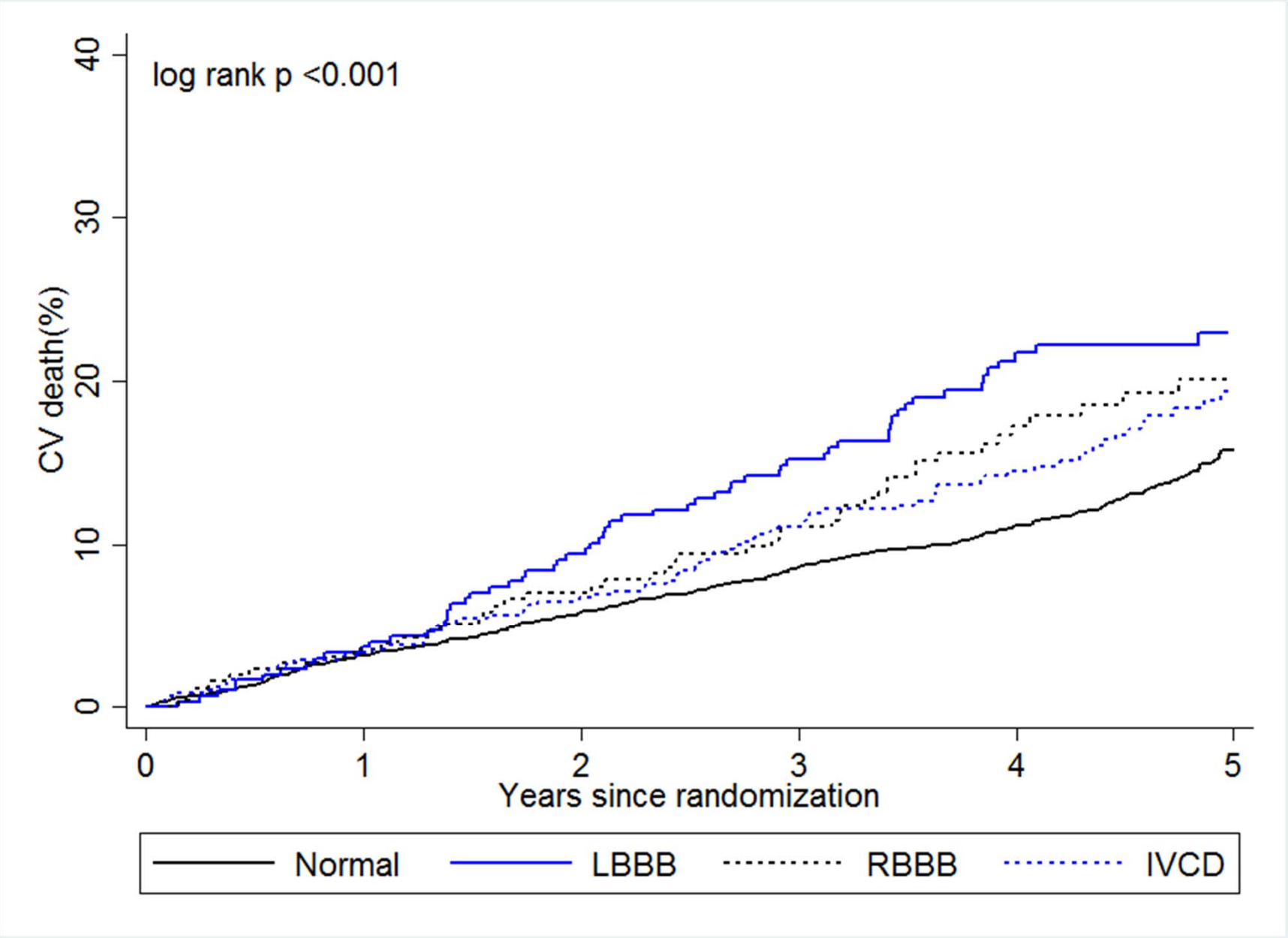

Figure 12. Kaplan-Meier curve of all-cause death according to QRS morphology category (4 subgroups)